

Effect of Plasma and Red Blood Cell Transfusions on Survival in Patients With Combat Related Traumatic Injuries

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Background: The amount and age of stored red blood cells (RBCs) are independent predictors of multiorgan failure and death in transfused critically ill patients. The independent effect of plasma transfusion on survival has not been evaluated. Our objective was to determine the independent effects of plasma and RBC transfusion on survival for patients with combat-related traumatic injuries receiving any blood products.

Methods: We performed a retrospective review of 708 patients transfused at least one unit of a blood product at one combat support hospital between November 2003 and December 2004. Admission vital signs, laboratory values, amount of blood products transfused in a 24-hour period, and Injury Severity Score (ISS) were analyzed by multivariate logistic re-

gression to determine independent associations with in-hospital mortality.

Results: Seven hundred and eight of 3,287 (22%) patients admitted for traumatic injuries were transfused a blood product. Median ISS was 14 (range, 9–25). In-hospital mortality was 12%. Survival was associated with admission Glasgow Coma Scale score, SBP, temperature, hematocrit, base deficit, INR, amount of RBCs transfused, and massive transfusion. Each transfused FFP unit was independently associated with increased survival (OR: 1.17; 95% CI: [1.06–1.29]; $p = 0.002$); each transfused RBC unit was independently associated with decreased survival (OR: 0.86; [0.8–0.92]; $p = 0.001$). A subset analysis of patients ($n = 567$) without massive transfusion (1–9 RBC/FWB units) also revealed an independent association be-

tween each FFP unit and improved survival (OR: 1.22; 95% CI: [1.0–1.48]; $p = 0.05$) and between each RBC unit and decreased survival (OR: 0.77; [0.64–0.92]; $p = 0.004$).

Conclusion: For trauma patients transfused at least one unit of a blood product, FFP and RBC amounts were independently associated with increased survival and decreased survival, respectively. Prospective studies are needed to determine whether the early and increased use of plasma and decreased use of RBCs affect mortality for patients with traumatic injuries requiring transfusion.

Key Words: Plasma, Red blood cells, Trauma, Mortality, Hemorrhage, Coagulopathy.

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Hemorrhage from traumatic injuries is the second most common cause of death and the most common cause of potentially preventable deaths from combat related injuries.^{1,2} Upon autopsy review, it was estimated that 15% to 20% of deaths that occur in combat were preventable with appropriate treatment, with 66% to 80% of these deaths occurring from hemorrhagic shock.^{1,2} Death from severe traumatic injuries occurs quickly, usually within 6 hours to 12 hours from hospital admission.^{3–6} Strategies or therapeutic principles that

can be rapidly applied have the potential to prevent death from hemorrhagic shock and have a significant impact on improving survival for patients with traumatic injuries.^{7,8}

According to Advanced Trauma Life Support guidelines, the standard approach to the resuscitation of patients with hemorrhagic shock includes the initial bolus of 2 L of crystalloid solutions and then red blood cell (RBC) transfusion.⁹ Plasma products are transfused based on the laboratory documentation of coagulopathy.⁹ This approach emphasizes the use of crystalloids and RBCs to potentially improve cardiac output and oxygen delivery and delays the use of plasma. Recent reports in the literature have documented adverse effects of excessive crystalloid use and the independent association of RBC transfusion with increased mortality in critically ill patients.^{10–24} There is also a lack of evidence that the transfusion of stored RBCs improves oxygen consumption for patients with an oxygen debt or who are in shock.^{17,20,25–27}

Current review articles describing damage control or hemostatic resuscitation principles, coupled with those describing the early coagulopathy of trauma,^{28–30} suggest a change from this classic approach maybe in order. Its goals for patients who are hypocoagulable or in shock with life threatening traumatic injuries are rapid surgical correction of large vessel bleeding, prevention and treatment of acidosis

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and hypothermia, transfusion of plasma, RBCs, and platelets in a 1:1:1 ratio, early use of fibrinogen, potential use of recombinant activated factor VII (rFVIIa), and decreased emphasis on excessive crystalloid and RBC use.^{31–35} Improved outcomes in severely injured and massively transfused (≥ 10 units RBCs) patients have been associated with the use of hemostatic resuscitation principles,^{7,8} but have not been studied in trauma patients requiring any amount of blood products. Our objective in this study was to determine the effect of fresh frozen plasma (FFP) and RBC transfusion on in-hospital survival for patients with combat-related injuries who required any blood product administration.

METHODS

We performed an IRB approved retrospective analysis of data from trauma patients admitted to one combat support hospital in Iraq between November 2003 and December 2004 using the Joint Theater Trauma Registry (JTTR) maintained at the US Army Institute of Surgical Research (USAISR) at Ft. Sam Houston in San Antonio, TX. Patients were included if they received one or more units of any blood product, including RBCs, FFP, and fresh whole blood (FWB). Data collected included patient age, admission vital signs (systolic blood pressure, heart rate, temperature) and laboratory values (base deficit, pH, hematocrit [HCT], International Normalized Ratio [INR]), Glasgow Coma Scale (GCS) Score, Injury Severity Score (ISS), rFVIIa use, and 24-hour amount of RBC, FFP, FWB units transfused. Mortality was measured at discharge or transfer from the combat support hospital in Iraq. Anatomic and physiologic cause of death was determined by one investigator (J.G.P.) on review of the chart and death certificate. Apheresis platelets were not available for transfusion during the study period; as a result FWB was transfused when platelets were indicated. Admission platelet concentrations were not recorded into the database. Massive transfusion was defined as ≥ 10 units of RBCs and FWB combined in 24 hours. Since the function of RBCs and plasma in FWB is likely to differ significantly than when stored as components, we did not include the contribution of each component from FWB in our analysis. Shock was defined as an admission base deficit of ≥ 4 or pH < 7.2 and coagulopathy as an INR ≥ 1.5 .

Statistical analysis was performed with SPSS 14.0 (Chicago, IL). Parametric data are presented as mean (\pm SD). Nonparametric data are presented as median (interquartile range). Statistical significance was set at a $p \leq 0.05$. Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis. Variables with $p < 0.2$ on univariate analysis were included in the regression model unless collinearity existed between variables. Receiver operating curve analysis was used to determine appropriate cut off points for continuous variables chosen to be modeled as binary. Despite collinearity between RBC and FFP units transfused, both variables were

included in the regression analysis because of clinical suspicion of potential independent effects on survival.

A secondary subset analysis that included only those who did not receive a massive transfusion was also performed to provide another method to determine whether the effects measured in the primary analysis were predominantly influenced by patients who received massive transfusions. Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis.

RESULTS

There were 3,287 patients admitted with traumatic injuries with a median ISS of 6 (IQR, 2–11) and in-hospital mortality of 4.4%. Of these patients, 708 (22%) were transfused a blood product. Median ISS was 14 (IQR, 9–25); in-hospital mortality was 12%. Median hospital length of stay was 3 days (IQR, 2–8) for all patients. Nonsurvivors died at a median of 1 day (IQR, 1–5) postadmission. Table 1 describes patient characteristics at admission. Base deficit or pH was recorded in 560 of 708 (79%) patients. The incidence of shock (base deficit ≥ 4 or pH ≤ 7.2) at admission was 356 of 560 (64%) for patients receiving blood products. INR was recorded in 346 of 708 (49%) patients. The incidence of coagulopathy (INR ≥ 1.5) at admission was 133 of 346 (38%) for patients receiving blood products. Base deficit, pH, or INR was recorded for 615 of 708 (87%) patients, and 409 of 615 (67%) of these patients were in shock or coagulopathic (Fig. 1). Primary surgical procedures were recorded for 647 patients. The most common procedures required for these 647 patients who required blood products were celiotomy 31%, craniectomy 16%, vascular repair 13%, and skeletal fixation 11%.

The amount and percentage of each blood product transfused is reported in Table 2. The mean age of RBCs transfused during the time period of this study was 33 days (± 6). The age of RBCs transfused was calculated in aggregate from the hospital blood bank database; the storage age of RBCs transfused to individual patients was not available. Variables

Table 1 Demographics of Patients With Traumatic Injuries Receiving Blood Products

Variables	All Patients Transfused (n = 708)	Patients Without Massive Transfusion (n = 567)
Male (%)	677/708 (96)	540/567 (95)
GCS score	(672) 15 (3–15)	(549) 15 (15–15)
SBP (mm Hg)	(701) 114 (± 28)	(562) 118 (± 25)
HR (bpm)	(706) 106 (± 27)	(565) 103 (± 26)
Temperature (°F)	(587) 96.9 (± 2.4)	(475) 97.3 (± 2.2)
Hematocrit	(683) 32.2 (± 8.3)	(547) 32.8 (± 8.2)
Base deficit	(560) 5 (2–10)	(435) 4 (2–8)
pH	(569) 7.28 (7.19–7.35)	(442) 7.3 (7.22–7.36)
INR	(346) 1.4 (1.26–1.63)	(260) 1.39 (1.26–1.58)
ISS	(708) 14 (9–25)	(567) 14 (9–22)

Data presented as (no.) mean (\pm SD), median (IQR) or as a percentage (%).

SBP indicates systolic blood pressure; HR, heart rate; ISS, Injury Severity Score.

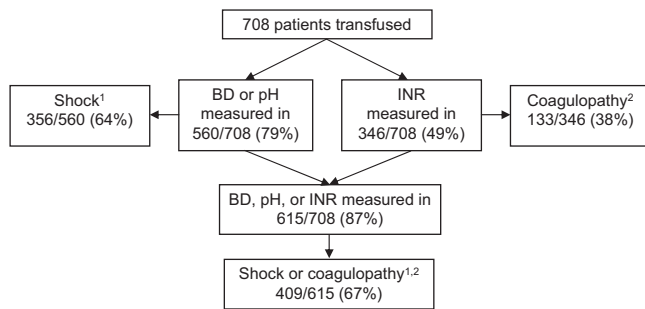


Fig. 1. Flow diagram of values measured indicating the incidence of shock and coagulopathy. BD, base deficit; INR, International Normalized Ratio. ¹Shock defined as base deficit ≥ 4 or pH < 7.2 . ²Coagulopathy defined as INR > 1.5 .

Table 2 The 24 h Total Amount and Percentage of Each Blood Product Transfused to All Patients Requiring Any Blood Product

Variable	24 h Total Amount	% Patients Receiving Blood Product
RBCs (U)	4 (2–7) [6]	687/708 (97%)
FFP (U)	0 (0–4) [3]	343/708 (48%)
FWB (U)	0 (0–0) [1]	99/708 (14%)
rFVIIa		49/708 (7%)

Data presented as median (interquartile range) [mean] or as percentage (%).

RBC indicates red blood cells; U, units; FFP, fresh frozen plasma; FWB, fresh whole blood; rFVIIa, activated recombinant factor VII.

associated with in-hospital survival included admission GCS score, SBP, temperature, HCT, and pH (Table 3). Variables associated with decreased in-hospital survival were admission heart rate, base deficit, INR, 24-hour amount of RBC units transfused, and percentage patients who received massive transfusion (Table 3). Logistic regression analysis included admission heart rate, GCS score, SBP, temperature,

HCT, base deficit, ISS, 24-hour total amount of RBC and FFP units transfused. Colinearity was measured between admission pH and INR with base deficit and also between RBC amount and massive transfusion. As a result, pH, INR, and massive transfusion were not used in the regression model. Each unit of FFP transfused was independently associated with improved in-hospital survival (OR: 1.16; [1.05–1.28]; $p = 0.003$), and each unit of RBC transfused was independently associated with decreased survival (OR: 0.84; [0.79–0.9]; $p = 0.001$; Table 4). Additionally, ISS, GCS score ≤ 8 , and base deficit ≥ 4 were each independently associated with decreased survival (Table 3). Area under the curve for this regression model was 0.81. When massive transfusion was replaced in the regression analysis for RBC amount it was independently associated with decreased survival (OR: 0.3; [0.16–0.84]; $p = 0.02$).

To determine whether the effects of individual blood products on survival were predominantly influenced by the patients who received a massive transfusion, a subset analysis of 567 of 708 (80%) patients who received blood products but did not receive a massive transfusion (< 10 units of RBCs and FWB combined) was performed. The percentage of the amount of all blood products transfused to these 567 patients compared with all 708 patients was 2,745 of 6,315 (43%). The percentages of each blood product transfused to these 567 patients compared with all 708 patients were as follows: 1,972 of 4,016 units (49%) RBCs, 730 of 1,801 (40%) FFP, and 43 of 498 (9%) FWB. Demographic data for patients who did not receive a massive transfusion is in Table 1. The amount and percentage of each blood product transfused for the 567 patients without massive transfusion is reported in Table 5. The variables associated with survival for these patients are indicated in Table 6. On multivariate logistic regression, each unit of FFP transfused was independently associated with survival (OR: 1.22; [1–1.48]; $p = 0.05$) and each unit of RBCs transfused was independently associated

Table 3 Univariate Analysis of Variables Associated With Survival in All Patients Requiring Any Blood Product

	Survived (n = 621)	Died (n = 87)	p
GCS score	15 (5–15)	3 (3–14)	< 0.001
Age (yr)	27 (± 11)	26 (± 10)	0.56
Heart rate (bpm)	115 (± 29)	105 (± 26)	0.001
SBP (mm Hg)	115 (± 26)	102 (± 34)	0.001
Temperature ($^{\circ}$ F)	97 (± 2.3)	96 (± 3)	0.02
Hematocrit	33.1 (27.1–38)	27.9 (21.4–35)	< 0.001
pH	7.29 (7.21–7.35)	7.16 (7.0–7.26)	< 0.001
Base deficit	5 (2–8)	13 (7–18)	< 0.001
INR	1.4 (1.25–1.6)	2.06 (1.59–2.9)	< 0.001
RBC (Units)	4 (2–6) [10]	7 (4–13) [5]	< 0.001
FFP (Units)	0 (0–4) [2.4]	2 (0–4) [3.8]	0.12
Massive transfusion	519/620 (83%)	48/86 (56%)	< 0.001
rFVIIa % use	43/621 (7%)	6/87 (7%)	0.99
ISS	14 (9–22)	21 (11–27)	< 0.001

Data presented as mean (\pm SD), or median (IQR).

GCS indicates Glasgow Coma Scale score; bpm, beats per minute; SBP, systolic blood pressure; RBC, red blood cells; U, units; FFP, fresh frozen plasma; rFVIIa, activated recombinant factor VII; ISS, Injury Severity Score.

Table 4 Multivariate Logistic Regression Analysis of Variables to Determine Independent Associations With Inhospital Survival for Patients Receiving One or More Units of a Blood Product in the First 24 h of Admission

	Odds Ratio (95% CI)	p
FFP (1 Unit)	1.16 (1.05–1.28)	0.003
RBC (1 Unit)	0.84 (0.79–0.9)	<0.001
GCS score ≤8	0.2 (0.1–0.38)	<0.001
Deficit ≥4	0.26 (0.11–0.62)	0.003
ISS	0.97 (0.95–0.99)	0.04

Additional variables included in the regression model were admission temperature, heart rate, systolic blood pressure, and hematocrit. Admission pH, INR and massive transfusion were not included because of colinearity with admission base deficit and RBC amount.

Area under the curve for regression model was 0.81.

ISS indicates Injury Severity Score; GCS, Glasgow Coma Scale score; SBP, systolic blood pressure; RBC, red blood cells; FFP, fresh frozen plasma.

Table 5 The 24 h Total Amount and Percentage of Each Blood Product Transfused to Patients Who Did Not Receive a Massive Transfusion in the First 24 h After Admission

Variable	24 h Total Amount	% Patients Receiving Blood Product
RBCs (U)	3 (2–5) [3]	544/567 (96%)
FFP (U)	0 (0–2) [1]	215/567 (38%)
FWB (U)	0 (0–0) [0.1]	18/567 (3%)
rFVIIa		13/567 (2%)

Data presented as median (interquartile range) [mean] or as a percentage (%).

RBC indicates red blood cells; U, Units; FFP, fresh frozen plasma; FWB, fresh whole blood; rFVIIa, activated recombinant factor VII.

Table 6 Univariate Analysis of Variables Associated With Survival for Patients Not Receiving a Massive Transfusion

	Survived (n = 519)	Died (n = 48)	p
GCS score	15 (5–15)	3 (3–6)	<0.001
Age (yr)	27 (11)	24 (11)	0.12
Heart rate (bpm)	103 (26)	108 (27)	0.21
SBP (mm Hg)	119 (24)	106 (34)	0.01
Temperature (° F)	97.3 (2.2)	96.4 (2.5)	0.04
Hematocrit (g/dL)	33 (7.9)	29 (10.1)	0.02
pH	7.3 (7.23–7.36)	7.2 (7.01–7.29)	<0.001
Base deficit	4 (1–8)	12 (7–17)	<0.001
INR	1.4 (1.26–1.54)	1.9 (1.6–2.3)	<0.001
RBC (Units)	3 (2–4)	5 (2–6)	0.003
FFP (Units)	0 (0–2) [1.3]	0 (0–2) [1.4]	0.8
rFVIIa % use	12/519 (2%)	1/48 (2%)	1
ISS	13 (9–21)	19 (10–27)	0.001

Data presented as mean (±SD), or median (IQR) [mean].

GCS indicates Glasgow Coma Scale score; bpm, beats per minute; SBP, systolic blood pressure; RBC, red blood cells; U, Units; FFP, fresh frozen plasma; rFVIIa, activated recombinant factor VII; ISS, Injury Severity Score.

Table 7 Multivariate Logistic Regression Analysis of Variables to Determine Independent Associations With Inhospital Survival for Patients Not Receiving a Massive Transfusion in the First 24 h After Admission

	Odds Ratio (95% CI)	p
FFP (1 Unit)	1.22 (1.0–1.48)	0.05
PRBC (1 Unit)	0.77 (0.64–0.92)	0.004
ISS	0.96 (0.93–0.99)	0.01
GCS score ≤8	0.18 (0.07–0.43)	<0.001
Base deficit ≥4	0.14 (0.04–0.48)	0.002

Additional variables included in the regression model were admission temperature, systolic blood pressure, and hematocrit. Admission pH and INR not included because of colinearity with admission base deficit.

Area under the curve for regression model was 0.83.

ISS indicates Injury Severity Score; GCS, Glasgow Coma Scale score; RBC, red blood cells; FFP, fresh frozen plasma.

Table 8 Primary Injury Location Associated With Death

Injury Location	All Transfused Patients (n = 75)*	Patients Without Massive Transfusion (n = 44)*
Airway	3/75 (4)	3/44 (6.8)
Head/neck	23/75 (31)	19/44 (43.2)
Chest	10/75 (13)	5/44 (11.4)
Abdomen	29/45 (39)	12/44 (27.3)
Pelvis	2/75 (3)	1/44 (2.3)
Extremities	7/75 (9)	3/44 (6.8)
Integument	1/75 (1)	1/44 (2.3)

Values inside parentheses are percentages.

* Injury location primarily associated with death available for 75 of 87 (87%) of all patients transfused and 44 of 48 (92%) for patients without massive transfusion.

Table 9 Physiologic Process Primarily Associated With Death

Physiologic Process	All Transfused Patients (n = 81)*	Nonmassive Transfused Patients (n = 45)*
Respiratory failure	4/81 (5)	4/45 (9)
Hemorrhage	35/81 (43)	10/45 (22) [†]
CNS	22/81 (27)	18/45 (40)
Body disruption	2/81 (3)	2/45 (4)
Sepsis	10/81 (12)	6/45 (13)
Multiorgan failure	8/81 (10)	5/45 (11)

Values inside parentheses are percentages.

* Physiologic cause of death available for 81 of 87 (93%) of all patients transfused and 45 of 48 (94%) for patients without massive transfusion.

[†]p is 0.02 for the comparison of death from hemorrhage between groups.

with decreased survival (OR: 0.77; [0.64–0.92]; p = 0.004) (Table 7). Other variables independently associated with decreased survival were ISS, GCS score ≤8, and base deficit ≥4. Area under the curve for this regression model was 0.83.

Anatomic and physiologic cause of death for both groups of patients analyzed are described in Tables 8 and 9. Head/neck

and abdominal injuries were the most common injury locations associated with death. Hemorrhage and CNS injury were the most common physiologic causes of death with the incidence of death from hemorrhage increased in all patients transfused compared with patients without massive transfusion.

DISCUSSION

This retrospective study is the first to indicate that the amount of plasma transfused to patients with traumatic injuries who require any amount of blood products is independently associated with improved in-hospital survival. A subset analysis of patients who did not require a massive transfusion also indicated an independent association between the amount of plasma transfused and survival. Both analyses indicate that even in trauma patients who did not receive massive transfusion increased plasma administration may improve survival. Previous studies have indicated that an increased ratio of FFP:RBC for patients requiring massive transfusion was independently associated with survival.⁷ Our results indicate that the amount of plasma transfused is independently associated with improved survival for patients with traumatic injuries requiring any amount of blood products.

An expected finding was that death from hemorrhage was the most common physiologic cause of death in all patients receiving blood products. The incidence of death from hemorrhage was decreased in patients without massive transfusion when compared with all patients despite similar admission base deficit, INR, hemoglobin, temperature, SBP, and ISS. It is possible that this reflects the influence of the 20% of patients who received a massive transfusion in the all patients transfused group. Massive transfusion itself was independently associated with death in our analysis. The independent effect of massive transfusion on decreased survival may be a result of dilutional coagulopathy and the effect of transfusing large amounts of aged RBCs (33 days) in this cohort.

Related to the independent effect of massive transfusion, we also confirm findings reported in other retrospective studies that increased RBC transfusion is independently associated with decreased survival.^{12–24} Our study is unique in that it also indicates that even for patients with traumatic injuries who do not receive a massive transfusion the amount of RBCs transfused is independently associated with decreased survival. Previous and appropriate criticism of many of these studies has been that the amount of RBCs transfused is an indicator of severity of injury that cannot be completely adjusted for by regression analysis. According to this theory, in our study, increased plasma transfusion should have also been transfused in increased amounts to those with increased injury and would have been independently associated with decreased survival. Our results after using regression analysis to adjust for confounding variables revealed opposite independent effects on survival for RBC and plasma transfusions. Since the amount of RBCs transfused was increased in nonsurvivors and independently associated with decreased survival, and the amount of FFP transfused was also increased

(numerically not statistically) in nonsurvivors but independently associated with improved survival, the argument that blood product transfusion is a indicator of severity of injury that cannot be adjusted for appears to be faulty. If increased amounts of blood product transfusion were simply a marker of injury severity, FFP should have also been independently associated with decreased survival caused by lack of ability to adequately adjust for all possible confounders. Our results indicate that it may be possible to adequately adjust for confounders to determine the effect of individual blood products on survival.

The use of stored whole blood declined in the 1980s as component therapy became standard of care primarily to improve resource utilization.³⁶ The indications for the use of plasma have been determined by estimates of plasma protein requirements based on calculation, animal studies, and clinical experience during the time when stored whole blood was primarily transfused.³⁷ Standard indications for the use of plasma have included either a 1 to 2 blood volume loss or an INR greater than 1.5 times above normal in a patient with active bleeding.^{38,39} These guidelines may be appropriate for postoperative bleeding in an otherwise healthy patient but may not be the optimal approach for trauma patients who are hypocoagulable or in shock.³⁷

A consistent definition of shock according to base deficit values is not well described. We chose to define shock as a base deficit of ≥ 4 because the normal range of base deficit is -3 to $+3$ and recent evidence published in a study of over 800,000 trauma patients that mortality starts to increase at a base deficit above 4.⁴⁰ Base deficit of ≥ 4 was also chosen for the cut off point in our regression analysis as a result of it being the value that was most accurate with predicting death by receiver operating curve analysis.

The majority 409 of 615 (67%) of patients in our study, in which base deficit, pH, or INR were recorded, were coagulopathic or in shock. The need for transfusion may also indicate that the patients who did not meet our definition of coagulopathy or shock may have been at risk for these conditions. Significant acidosis (base deficit >6) and severe trauma (ISS >15) are both independently associated with coagulopathy and death in trauma patients.^{29,41} Additionally, a recent study provides data that suggests hypoperfusion, indicated by an increased base deficit, may cause coagulopathy by increased activated protein C.²⁸ Increased plasma for our patients either at risk of coagulopathy or who are already coagulopathic would potentially counterbalance the activation of protein C, which would prevent or treat a hypocoagulable state and prevent death from hemorrhage.

Damage control or hemostatic resuscitation principles advocate not only for the aggressive correction of coagulopathy and shock but also the prevention of coagulopathy and shock in those at risk.^{31,33,38,42} Early and increased plasma transfusion has the potential to effectively prevent or treat coagulopathy and shock by improving hemostasis and volume expansion.^{10,37,38,42} Each unit of FFP in addition to

coagulation factors contains 0.5 g of fibrinogen.³⁷ Recent studies suggest that fibrinogen administration is essential for achieving hemostasis in patients with significant traumatic injuries^{43–48} and very likely contributes to the improved outcomes that have been associated with increased transfusion of plasma.^{7,49,50} However, the use of plasma as a volume expander is controversial though this practice has been relatively abandoned since the 1940s.³³ Volume expansion for hypovolemic patients in hemorrhagic shock is required to improve cardiac output by maintaining preload. Plasma additionally acts as a buffer and may benefit through improvement of acidemia.⁵¹ Recent analysis of hemodynamic and acid base data indicates that type specific plasma improves survival compared with other colloid and crystalloid solutions potentially as a result of adequate volume expansion and hemorrhage control in animal experiments.⁵² Conversely, in other animal experiments, RBC use was associated with decreased cardiac output and mean arterial pressure when compared with plasma containing whole blood.⁵³ Additionally, RBC transfusion did not improve cardiac function in another study in which animals were initially resuscitated with crystalloids.⁵⁴ Direct comparisons between FFP and RBC transfusions as volume expanders have not been performed, but the existing evidence supports that FFP may be superior in improving cardiac output. We agree with the concept of limiting indiscriminate use of plasma as a volume expander; however, for the group of casualties who initially present with coagulopathy and/or shock from injury and blood loss, plasma is likely the optimal resuscitation fluid especially when the alternative is stored blood of advanced age or crystalloid. Prethawed plasma was not used during the time period of this study. Experience since then has demonstrated the benefits of immediate availability of prethawed plasma.

The volume expansion effect of either plasma or RBCs will improve oxygen delivery by increasing preload and cardiac output, which will at the very least increase the delivery of the patients own hemoglobin to microvascular tissues. The predominant use of RBCs in hypovolemic trauma patients with significant injuries contributes to development of a dilutional coagulopathy and may increase the risk of receiving a massive transfusion, which itself is associated with increased mortality.⁵⁵

The rationale for predominantly transfusing primarily RBCs for patients in hemorrhagic shock has been to improve oxygen delivery and consumption. The ability of transfused RBCs to improve oxygen consumption for patients in shock may be dependent on its storage age. Animal and human studies indicate that increased RBC storage time is associated with decreased microvascular perfusion or the inability to increase oxygen consumption for subjects in an oxygen dependent state.^{26,56–58} Transfused hemoglobin from older stored RBCs (>14 days) may not be able to improve oxygen delivery to increase oxygen consumption for patients in shock as a result of storage lesion effects. These effects include decreased RBC deformability, increased inflammatory injury,

decreased nitric oxide available at the microvascular level, and increased adhesion and aggregation of RBC to endothelial cells and to other RBCs, respectively.^{12,17,20,23,24} More importantly in animal and human studies of patients in shock, microvascular perfusion and oxygen consumption remains the same or decreases with RBC transfusion.^{8,17,25–27,59} The importance of the effect of RBC storage age on outcomes in critically ill patients is highlighted by the fact that the average age of transfused RBCs in the United States is 22 days⁶⁰ and multiple studies have indicated that the age of RBCs transfused is associated with increased morbidity and mortality in the critically ill.^{18,22,61} The independent association of the amount of RBC transfusions with decreased survival may be related to the increased storage age of RBCs transfused to all patients in our study (33 days). The mean storage age of RBCs transfused per patient was not able to be analyzed as a variable associated with survival since this data were not recorded per patient.

Anemia and hypotension associated with traumatic injuries have both been associated with increased morbidity and mortality,^{14,62} but interestingly, the treatment of mild to moderate anemia and hypotension with the transfusion of stored RBCs for trauma patients has not been associated with improved outcomes. Even in patients with acute coronary syndrome, effects of RBC transfusion on mortality have been contradictory and may indicate older patients may benefit from higher RBC transfusion triggers.^{63,64} The use of stored RBCs, instead of whole blood, to resuscitate trauma patients has been practiced for decades. Its ability to acutely resuscitate patients is unquestioned. If the patient survives the initial 6 hours to 12 hours of resuscitation and hemostasis, the storage lesion of RBCs may cause the increased morbidity and mortality that has been documented with increased RBC use. The effect of the RBC storage lesion on morbidity and mortality in critically ill patients needs prospective study to determine causality. Prospective trials are needed to evaluate if the transfusion of RBCs of decreased storage age (<14 days) for trauma patients in shock would improve outcomes. The ability of prestorage leukoreduction and RBC washing to improve outcomes for critically ill patients has been contradictory and also requires further study.^{24,65,66} A balanced approach of all blood components in a 1:1:1 ratio, with the use of RBCs less than 14 days of storage, may be the optimal empiric resuscitation approach for patients with hemorrhagic shock.^{7,31,33,42,67,68}

Increased plasma transfusion for patients bleeding with traumatic injuries may increase risks associated with its use. Significant risks associated with plasma use include transfusion related acute lung injury and nonhemolytic transfusion reactions.⁶⁹ Inappropriate and excessive use of plasma will also increase the risk of volume overload. There is also the potential for increased serious thrombotic events with increased plasma use for trauma patients who present with local bleeding but are globally hypercoagulable.^{70,71} These risks compared with potential benefits of increased plasma trans-

fusion require further study for patients with significant bleeding from traumatic injuries.

Our study is limited by its retrospective nature, which may not have accounted for all factors associated with survival. As it takes a significant amount of time to thaw frozen plasma, there may be a survival bias for patients who receive plasma as they need to survive long enough to have this product issued and transfused. A significant limitation was the lack of admission platelet concentration in our analysis. These values were not recorded in the database used for this study. In addition, 30-day mortality was not able to be calculated since many foreign nationals were transferred once stable to other medical facilities. Since the median time to death for nonsurvivors was 1 day (1–5 days) and we used 24-hour amount of each blood product, we were measuring the effect of blood products given in the initial resuscitation on short term or acute mortality. Total blood products transfused within the first 30 days of admission would be required to more accurately determine their effect on 30-day mortality. Future retrospective studies should include admission platelet concentration values to more completely adjust for all potential variables associated with survival. Despite the recognized limitations of our study, prospective animal hemorrhagic shock studies evaluating the appropriate balance of plasma and RBC transfusions to improve both coagulopathy and shock are warranted. The effect of plasma and stored RBC products on oxygen delivery by improving volume expansion and the effect of storage on all blood products requires further study.

CONCLUSIONS

In trauma patients requiring blood products, increased transfusion of plasma independently improved survival and increased transfusion of RBCs independently decreased survival. These effects on survival for both plasma and RBCs were also measured in patients who did not receive a massive transfusion. Individual blood product use can be both associated with severity of injury and adequately adjusted for in retrospective studies to analyze for their independent effects on mortality. Prospective studies are needed to determine whether hemostatic resuscitation strategies that support the early and increased use of plasma and decreased use of RBCs affect mortality for patients with traumatic injuries requiring transfusion.

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DISCUSSION

Dr. Martin A. Schreiber (Department of Surgery, Section of Trauma and Critical Care, Oregon Health & Science University, Portland, OR): In this very important article, the authors have documented predictors of survival in combat victims receiving blood transfusions. The primary finding of this study is that increased mortality is associated with each unit of RBC transfused and increased survival is associated with each unit of fresh frozen plasma transfused. These results are very significant but do they reflect reality? I have a number of comments and questions for the authors:

1. The data are 3 years to 4 years old and it reflects older practices like absence of platelet availability, limited rFVIIa use (7% of patients) and no mention of cryoprecipitate or thawed plasma. The sophistication and application of hemostatic resuscitation has advanced tremendously in the intervening period. Are the results still pertinent? The failure to record platelet counts in the database is extremely unfortunate.
2. The authors have limited their evaluation to a 24-hour period. What is the basis for this as the need for ongoing transfusion may also be indicative of outcome?
3. The authors state that the amount of FFP transfused was increased in nonsurvivors but at the same time they state that increased FFP transfusion is independently associated with improved survival. How can this be possible? This is obviously a key point as they use this argument to prove that the association between increased RBC transfusion and mortality is not simply because patients who received more blood were more injured. Wouldn't this data be better represented by correlating the ratio of plasma:RBC transfusion with survival?
4. The primary endpoint of this study is hospital mortality. This significantly limits its utility especially in the case of coalition patients who are rapidly evacuated. The authors have access to the Joint Theater Trauma Registry. Why didn't they use 30-day mortality?
5. Shock was defined as a base deficit >4 or a pH <7.2 . How were these numbers chosen? A base deficit of 4 correlates with a pH higher than 7.2 in a patient with a normal P_{CO_2} .
6. Fresh whole blood was used in this study. What was its effect on mortality? Were the RBCs and plasma in the fresh whole blood included in the authors' statistical models? This should be clarified in the methods.
7. How do the authors explain the fact that there are no demographic differences between all patients transfused and patients who did not receive a massive transfusion as shown in Table 1?

Dr. Philip C. Spinella (Connecticut Children's Medical Center, Hartford, CT): Dr Schreiber, we thank you for your thoughtful comments and questions. Please allow me to address each of them specifically.

1. We agree that the failure to include admission platelet concentration in our analysis is a significant limitation although in MAJ Jeremy Perkins' analysis of over 400 patients with massive transfusion presented at this conference, admission platelet concentration was not independently associated with 48-hour or 30-day survival. Additionally, other retrospective analyses of variables independently associated with outcomes for patients with traumatic injury have not identified admission platelet concentration as a significant variable. Regardless, we do agree that the omission of this variable was unfortunate. Despite the data being mainly collected in 2004, we do think this data are pertinent primarily since it is intended to be hypothesis generating data and not hypothesis testing data. Our results will hopefully promote prospective studies in animal models regarding the optimal transfusion approach to address coagulopathy and shock secondary to trauma, which will also include the storage age of each product evaluated. Cryoprecipitate was used but at such a low amount that its inclusion would not have added any meaningful data to the article. Prethawed plasma was not used during the time period of this study.
2. The basis for including 24-hour total amounts of each blood product transfused was primarily because this was the only amount recorded in the database for this population. Our primary objective was to determine the effect of blood products transfused for the initial resuscitation of patients with traumatic injuries. Since the median (IQR) of hospital length of stay for all patients was 3 (2–8) days and the median time to death was 1 (1–5) day, our analysis on the effect of 24-hour amount of blood products is on acute mortality and does not represent effects on causes of mortality that occur beyond that point. We agree that the total amount of blood products transfused would be another important variable to analyze to determine whether additional products given after the initial resuscitation also effect outcomes. I will add the above data to the manuscript.
3. Our intention was to analyze the individual effect of each product transfused which is why we chose not to determine the effect of the plasma:RBC ratio on survival. There wasn't a statistical difference between the amount of plasma transfused between survivors and nonsurvivors in both analyses performed despite a small numerical increase in nonsurvivors in the primary analysis. It is possible for there to be transfusion of similar

amounts of plasma to survivors and nonsurvivors but still be independently associated with improved survival after adjusting for all other variables associated with survival. This is possible since lower GCS score and increased base deficit, ISS, and RBCs transfused independently contributed to the increased mortality to all patients including the nonsurviving patients who received plasma. The regression analysis revealed that despite similar amounts of plasma in survivors and nonsurvivors its increased use was independently associated with improved survival.

4. This dataset was developed as an adjunct to the JTTR and includes Iraqi foreign nationals who were often transferred to Iraqi facilities after their injuries were stabilized, before 30 days from injury. As a result 30-day mortality could not be calculated. There are currently not enough ISS calculated for patients in the JTTR to perform this analysis. We plan on

repeating the analysis on a larger dataset with the variables suggested as soon as possible.

5. There is no consensus in the literature regarding cut off values of any laboratory tests to define a shock state or oxygen debt. Only base deficit and serum pH were available in the database and these values were arbitrarily determined by the authors based on consensus.
6. In this cohort, including all patients requiring a transfusion, the amount of FWB did not affect survival. Since the function of RBCs and plasma in FWB is likely to differ significantly when stored as components we did not include the contribution of each component in our analysis. We will clarify this in our methods.
7. The lack of a difference in demographics between all transfused and the nonmassive transfusion patients was likely because 80% of the patients in this study did not receive a massive transfusion.